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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,683	11/15/2001	David Botstein	P2730P1C32	4971

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,683	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The Response and Information Disclosure Statement, submitted 30 June 2006, have been entered. Claims 1-118 and 124 are cancelled.

Claims 119-123 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Maintained/New Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 119-123 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under 35 U.S.C. § 101 are set forth at pages 2-9 of the previous Office Action (5 January 2006). Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (5 January 2006), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (*Remarks/Arguments*, 30 June 2006, page 3 and throughout) that the data presented in the instant Specification are enabling for the cognate antibody of the polypeptide of SEQ ID NO: 351. They argue that the PRO1153 nucleic acid is a diagnostic marker for several lung cancer tissues, and point to the results of the DNA amplification assay (page 6, 30 June 2006 and Specification, Table 9B).

Applicant's arguments (30 June 2006) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing a very small increase in DNA copy number- about 2.5 fold- in two cancerous tissues (see Table 9B). However, there is no evidence regarding whether or not PRO1153 mRNA or polypeptide levels are reliably increased in these cancers. Furthermore, as discussed in the previous Office Action (5 January 2006, page 9), what is often seen is a *lack* of correlation between and among DNA amplification, mRNA, and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease.

However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Given the small increase in gene copy number of PRO1153, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in chromosome copy number would correlate with significantly increased mRNA or polypeptide levels. Further research needs to be done to determine whether the small increase in PRO1153 DNA supports a role for the antibody in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

Accordingly, the Specification's assertions that the claimed PRO1153 antibodies have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

There is no evidentiary support that PRO1153 is involved in the etiology of cancer in the minority of lung tumor samples disclosed in the instant Application. Furthermore, as noted above, the increase in PRO1153 DNA in some lung tumor tissues and not others, (see Table 9B) points away from its role in a disease. At any rate, a positive result rate of about 20% is too low to make a conclusion about PRO1153 and cancer. Additionally, the *specific* function of the PRO1153 polypeptide has not been disclosed by Applicants or by recent research.

As discussed in the previous Office Action (5 January 2006), a 2-fold increase in gene copy number is not large and may be less likely to indicate disease (Hu, et al, 2003, Journal of Proteome Research 2:405-412), or may be sufficient (Applicant's Response, page 6). However, the type or magnitude of increase is not at issue in this case. All that is known about the PRO1153 antibody made to the PRO1153 peptide is that its associated gene may be increased in copy number in some cancerous tissues. It cannot be determined what the function of the protein is in the tissue; certainly the tissues provide no clues. It is hard to conceive of a specific and substantial utility for an antibody that binds to a protein for which no data or information is given.

Because Applicants do not know the function of the PRO1153 polypeptide, or if it is expressed in certain cancers, *detecting* (by use of the claimed antibodies) the PRO1153 polypeptide has no specific or substantial utility, since it is not useful to detect a protein for which a function has not yet been identified, and additionally might be expressed in a minority of cancers of one type. Since the asserted utility for the PRO1153 antibody is not in currently available form, the asserted utility is not substantial.

In the Response of 30 June 2006 (p. 6), Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (1994) and Lewin, B. (Genes VI, 1997) to support the statements of Dr. Polakis (Declaration of 30 June 2006). Applicants also cite numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al.,

Munaut et al., etc.). Applicants assert that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicants also contend that the references and the Polakis Declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While the examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (Alberts, 1994, p. 453). Meric et al. (as recited above) states the following:

"The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also go on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971 of Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in

the components of the translation machinery (see pages 973-974). Applicants have provided a number of references in support of the assertion that changes in mRNA levels correlate with changes in protein levels. However, with the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by the Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and which accurately describe general trends, specifically: Haynes (80 proteins examined) and Chen (165 proteins examined) (cited previously by Examiner).

With regard to the Orntoft reference, for example (Remarks, p. 7), Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one. Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. Instead, they concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). An analysis such as this was not done for PRO1153 in the instant specification. That is, it is not clear whether or not PRO1153 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any, of Orntoft et al. is not clear.

Applicants argue that there are numerous studies which support the contention that mRNA levels correlate with protein. For example, Applicants assert that Futcher et al. (1999) conducted a study of mRNA and protein expression in yeast and report a good correlation between protein abundance, mRNA abundance, and codon bias. Applicant's arguments have been fully considered but are not found to be persuasive. Futcher et al concludes that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins [emphasis added]" (p. 7368, col 1). Futcher et al. also admits that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion. Futcher et al. indicates that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (p. 7367, col 1, 1st full paragraph).

The examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a change in the mRNA level. However, *changes* in mRNA expression frequently do not result in *changes* in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO1153. The specification simply discloses that PRO1153 DNA is amplified in two primary lung tumors as compared to DNA levels in normal lung. There are no teachings in the specification as to the differential expression of PRO1153 mRNA in the progression of lung cancer or in response to different treatments of hormones (for example). Therefore, the examiner maintains that Applicant's measurement of an increase of PRO1153 DNA does not provide a specific and substantial utility for the claimed antibody.

The Declaration of Dr. Polakis, filed under 37 CFR 1.132 (30 June 2006), is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action because:

Applicants refer to the Declaration of Dr. Polakis and argue that mRNA is indicative of protein levels and therefore that the instant specification discloses a specific and substantial utility for the PRO1153 polypeptides of the current application and thus discloses a real-world utility for the anti-PRO1153 antibodies (p. 5, Remarks).

Applicants' arguments have been fully considered but have not been found to be persuasive. Utility requires that the skilled artisan be able to use the claimed invention. The specification does not provide a specific and substantial or a well-established use. A utility of being a diagnostic target for two lung tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use. This is not a substantial utility. In Table 9B, Applicants teach that PRO1153 DNA was higher in two lung-tumor tissues as compared to the normal tissues (page 142-143 of Specification). The important issue is that there is no guidance in the specification as to how high the levels of overexpression are relative to control. The Declaration of Dr. Polakis does not teach the level of reproducibility or the level of reliability of the results. Neither the specification nor the Declaration provides any evidence that indicates what the differences were. If a clinician took a tissue sample from a patient with suspected cancer, what is the likelihood that when compared with normal tissue, the level of nucleic acid of SEQ ID NO: 351 from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the normal tissues have to be a pooled sample or could it be from a single individual? Applicants have provided no indication of

the nature or number of samples that were used. The only thing Applicants teach is that the gene was "more highly expressed." This does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of tumor tissue that can be used, and other questions, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary. Furthermore, since no specific or substantial Utility has been demonstrated by the disclosed nucleic acids and polypeptides, there would be no reason to detect the polypeptide of SEQ ID NO: 351. Similarly, there would likewise be no reason to apply an antibody or ligand of the PRO1153 peptide as a method to treat cancer.

Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only the conclusions of Dr. Polakis are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease

(see discussion section).

Dr. Polakis (Declaration filed under 37 CFR § 1.132, 30 June 2006) states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in control tissues and that antibodies have been developed that identify and could possibly be used to downregulate the PRO peptides. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide (as discussed in the Remarks, page 4). He characterizes the instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. It has not been shown that protein levels are increased in these tissues. For these reasons, the Declaration is insufficient to overcome the rejection of Claims 119-123 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Doctor Polakis' conclusions are provided in the declarations. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA Levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. See Hu et al. (2003, Journal of Proteome Research 2:405-412) as discussed above.

Along with the second Declaration by Dr. Polakis (Polakis II), Exhibit B presents purportedly evidentiary data which identifies 28 gene transcripts out of 31 gene transcripts that showed "good correlations" between tumor mRNA and tumor protein levels.

Exhibit B and the Polakis II Declaration indicate that 31 antibodies have been used to quantitatively determine the level of tumor antigen proteins in both human tumor tissue and normal tissue, and the levels of mRNA and protein in both the tumor and normal tissues have been quantitatively compared (item 4). According to Applicants, Exhibit B shows that of the 31 genes overexpressed in human tumor tissue at the mRNA level, 28 of them are also detectably overexpressed in human tumor tissue at the protein level. Thus, according to Applicants, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded thereby (item 5). The Declaration further indicates that, based on personal scientific opinion, an increased level of mRNA in a tumor tissue relative to a normal tissue more often than not correlates to a similar increase in abundance of the encoded protein (item 6). This has been fully considered but is not found to be persuasive because PRO1153 does not appear in the table of Exhibit B, and thus, it is unclear how the result in Exhibit B is related to the present PRO1153. Further, the Declaration provides no information as to what those tumor antigens that do correlate (mRNA and proteins levels) have in common, and in the absence of such, one may not extrapolate that the PRO1153 would share the same characteristics as those tested. Furthermore, even if the result is relevant, there is no numerical data on what significant overexpression is, but "+" or "-", wherein "+" merely means "detectably" overexpressed as explained in the declaration. As such, the examiner could not independently evaluate the results. For example, how many tumor samples were analyzed, and how many normal tissues? How

many of the tissues comprise PRO1153? What are the levels of expression of the PRO1153 mRNA/protein in cancer vs. non-cancerous tissues? What does the "detectably overexpressed" level really means, and is it statistically meaningful? Furthermore, the fact that some samples showed no correlation is consistent with what the prior art has established, i.e., it is not predictable whether an increase of mRNA expression of a specific gene is correlated to the increase of the protein levels.

Therefore, in the absence of any evidence directly associated with the claimed PRO1153, and a knowledge of what those (in Exhibit B) that do correlate have in common, the Declaration and exhibit are insufficient to overcome the rejections of the claims under 35 U.S.C. 101, and 35 U.S.C. 112, first paragraph.

With respect to Dr. Polakis's personal scientific opinion, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not the increased mRNA levels is predictive of increased protein levels. (2) The instant specification only discloses the measurement of PRO1153 chromosomal DNA, and does not disclose any information regarding PRO1153 protein levels. There is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., the Chen reference (cited in the previous Office Action), which reports only 17% of 165 polypeptide spots or 21% of the genes had a significant

correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, factual support for the expert's opinion is absent as data disclosed in the Declaration is not related to the presently claimed PRO1153, the statistical significance of the result from other normal tissue genes is unclear, and no numerical data are included in the Declaration so that the examiner could independently evaluate them. As such, the Declaration of Dr. Polakis under 37 CFR 1.132 is insufficient to overcome the rejections of the claims under 35 U.S.C. 101, and 112, first paragraph.

Applicants discuss (Remarks, 30 June 2006, page 13 and throughout) points from case law in reference to the utility rejection, most of which the examiner agrees with. However, the fact patterns of the cases cited have little connection with utility/enablement as applied to the instant Application. Whatever the asserted specific utility might be - diagnosis of cancer, for example- it is **not** "more likely than not" (In re Oetiker, 1992, 977 F2d 1443, 1445, 24 USPQ2d), since the increase in DNA was found in only about 1/4 of lung cancer samples, and furthermore no statistical calculations were performed.

Applicants argue (Response, 30 June 2006, page 14 and throughout) that even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Applicant argues that the disclosure of the PRO1153 peptide can be viewed as providing a public benefit. However, the instant Specification does not provide specific information about the PRO1153 nucleotides, peptides or antibodies and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the peptides

is not in currently available form, the asserted utility for the antibodies is not substantial.

Conclusion

No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
11 September 2006

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER